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The Impact of Drug Vintage on Patient Survival: A Patient-Level Analysis Using Quebec's Provincial Health Plan Data

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ABSTRACT

Objectives: There is some debate about the value received for the money spent on prescription drugs. Some argue that most drug spending is on "me-too" drugs—drugs that provide only marginal health gains. Others suggest that the opposite is true—new drugs offer good value for money and are well worth the cost. To provide evidence on this issue, we evaluated the impact of drug innovation on the longevity of Canadians.

Methods: We analyzed patient-level claims data from Quebec's provincial health plan. We selected elderly patients with continuous health coverage dispensed at least one drug prescription in each year of the study period, 1997 to 2006. Drug vintage was defined as the active ingredient's earliest marketed date. We estimated the impact of drug vintage on patient survival using a time-varying Cox proportional hazards model that controlled for year indicator variables, patient age, sex, region of residence, low income status, medical services use, concomitant drug use, and comorbidities.

Results: Of the 102,743 subjects in the study population, 14,154 (14%) died during the study period. Mean patient age was 68 years; 59% were women. Our survival models indicated that the use of newer medications was associated with a statistically significant mortality risk reduction (hazard ratio: 0.522; 95% confidence interval: 0.476 to 0.572, $P < 0.0001$), relative to older medications. Other covariates associated with an increased risk of mortality included age, sex (male), low guaranteed income supplement status, hospitalization, and number of comorbidities.

Conclusion: This analysis showed that recent drug innovation has had a significant beneficial impact on the longevity of elderly patients.

Keywords: Canada, drug innovation, longevity, pharmaceuticals, survival.

Introduction

There is some debate about the value received for the money spent on prescription drugs. Most drug expenditure growth in Canada is due to substitution of newer for older medications. Some argue that most drug spending is on "me-too" drugs—medications that provide only marginal health gains [1]. Canada's Patented Medicine Prices Review Board classified 89% of the new active substances introduced over the period 2001 to 2006 as offering only limited or no therapeutic advantages over existing drugs [1]. Others suggest that the opposite is true—spending on new drugs has contributed to the 11-year gain in life expectancy in Canada during the last 50 years [2] and thus represents good value for money [3,4]. For instance, recent innovation in cancer therapy has had considerable impact, not only in cancer care and survival, but also in quality of life improvement for cancer patients [5–7]. Similar findings were also reported in other disease areas, such as human immunodeficiency virus (HIV) and cardiovascular disease (CVD). For instance, Lichtenberg showed that new drugs played a key role in a sharp decline in the number of US deaths caused by HIV from 1995 to 1998 [8,9]. With respect to CVD, Cutler et al. reported that the use of new drugs to manage hypertension and hyperlipidemia and to dissolve blood clots have markedly reduced CVD morbidity and mortality [10]. More recently, it was estimated that average blood pressures in the US for 1999 to 2000 would have been 10% to 13% higher without the use of antihypertensive drugs [11]. The authors also reported that 86,000 excess premature deaths from CVD would have occurred in 2001 if these drugs were not on the market [11]. New treatments also have the potential to reduce costly hospitalization admissions [12–14].

Some of the methods and particularly the aggregate nature of the data used in the literature of drug innovation have been criticized [15]. As far as we know, detailed individual-level data, allowing to control for other determinants of patient health outcomes and nondrug health-care costs that could be correlated with the use of newer treatments, have not been used yet to document potential gains from drug innovation in Canada. Studies using individual patient-level survival data yield compelling estimates of the impact of drug innovation on longevity for several reasons. First, these data allow researchers to better control for other determinants of longevity that might be correlated with drug innovation, such as age, sex, medical resources utilization, and comorbidities. Second, these data lend themselves to more precise measurement of drug consumption. Finally, analyses of individual-level data are less liable to various statistical problems, such as nonstationarity. The problem of nonstationarity in aggregate time series occurs when there is no long-run mean to which the longitudinal data returns. Because the standard econometric theory is derived under the assumption that variables of concern are stationary and the error term has zero expected value, standard techniques are invalid in the presence of nonstationary data. The level of gross domestic product is an example of nonstationary time series, as its mean value constantly increases over time.

This study therefore used patient-level survival data to estimate the impact of drug innovation on longevity. We modeled the

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survival of senior residents of the province of Quebec, from several birth cohorts who were afflicted with a variety of health problems. Survival hazards were modeled semiparametrically as a function of the vintage of the prescription drugs used (following Lichtenberg 2004) [16] as well as controls for a variety of factors unique to the patient (age, sex, indicator of low income, region of residence, disease status) and their use of other health services (hospitalization and physicians services). Briefly, we found evidence that drug vintage has a marked effect on survival, with newer drugs leading to increased longevity, especially for the treatment of asthma and CVD.

Patients and Methods

Hazard Model

The impact of drug innovation on longevity, conditional on time-varying patient demographic characteristics, use of medical services, and the nature and complexity of disease was estimated using a semiparametric hazard model. This technique models the hazard or the instantaneous probability of dying at any point in time among those who are still alive at that time. Such model allowed us to handle censored observations and appropriately model the dependent variable (survival), which is usually non-normally distributed. Although there are no assumptions made about the shape of the underlying hazard function, this approach assumes a multiplicative relationship between the probability of dying and the log-linear function of the covariates, also referred to as the "proportionality" assumption. In practical terms, this model assumes that given two observations with different values for the covariates of interest, the ratio of the hazard functions for those two observations does not depend on time.

Data Source

Medical and pharmacy claims data from Quebec's provincial health plan, *Régie de l'assurance maladie du Québec* (RAMQ), from January 1997 to December 2006 were used in this analysis. Data elements were drawn from four RAMQ databases: 1) *Information personne assurée*, patient demographic characteristics; 2) *Périodes d'admissibilité*, patient eligibility and type of coverage; 3) *Services pharmaceutiques*, outpatient prescription drug dispensing; and 4) *Services médicaux*, medical services billed. The four RAMQ databases are linked via a unique and encrypted patient identifier and allow longitudinal follow-up of patients. Information on the vintage of drug ingredients was drawn from the Health Canada *Drug Product Database* (available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php).

Drug Vintage Definition

We elected to define drug vintage as the earliest date of sale reported for each ingredient contained in the drug. Hence, if the drug was a combination of ingredients (e.g., hydrochlorothiazide, a combination of angiotensin-converting enzyme inhibitor and diuretic in the control of hypertension), each ingredient contained in the drug was separately considered as a prescription with its own drug vintage. The Health Canada *Drug Product Database* contains the marketed date of each active ingredient for each drug product. This marketed date is reported by pharmaceutical companies (notification is mandatory) to Health Canada.

Following the approach proposed by Lichtenberg [16], we generated the following drug vintage variables to assess the impact of drug innovation in the analysis:

- Pre-1970: the proportion of a patient's drug prescriptions made of active ingredients dated before 1970;
- Post-1970: the proportion of a patient's drug prescriptions made of active ingredients dated after 1970;
- Post-1980: the proportion of a patient's drug prescriptions made of active ingredients dated after 1980;
- Post-1990: the proportion of a patient's drug prescriptions made of active ingredients dated after 1990.

The "Pre-1970" period was the reference category in the regression analysis. In this context, because we used a cumulative distribution approach to formulate the drug vintage covariate, the parameter estimate associated with the variable "Post-1970" may be interpreted as the "marginal benefit" associated with the consumption of only 1970s versus Pre-1970 medications; the coefficient associated with the variable "Post-1980" may be interpreted as the "marginal benefit" associated with the consumption of only 1980s versus 1970s medications; and the coefficient associated with the variable "Post-1990" may be interpreted as the "marginal benefit" associated with the consumption of only Post-1990 versus 1980s medications. The cumulative impact on the hazard of dying of all Post-1970 medications relative to only Pre-1970 ingredients can be determined by adding the three coefficients (i.e., $\beta_{\text{Post-1970}} + \beta_{\text{Post-1980}} + \beta_{\text{Post-1990}}$).

Other Determinants of Survival

The other covariates used for adjustment in the regression model were year indicator variables and patient-specific demographic characteristics (age, sex, and region of residence), government guaranteed income supplement (GIS) status (an indicator of low income), medical resources utilization, drug utilization, and comorbidities.

The variables controlling for medical services use were stratified by inpatient and outpatient services. For the inpatient setting, we included two covariates in the model: a variable indicating the number of inpatient admissions for each calendar year and a variable indicating the total hospital length of stay (days) during the calendar year. For the outpatient setting, we controlled for the number of outpatient consultations to any physician and for the occurrence of consultations to a specialist (yes/no) during the calendar year. With respect to drug use, we controlled for the number of pharmacy claims observed during the calendar year, after adjusting the prescription length to 28 days per prescription.

Lastly, following the approach proposed by Lichtenberg [16], we inserted two categorical covariates to control for the nature of the person's illnesses in our model. First, we used the International Classification of Diseases, Ninth revision (ICD-9) diagnosis codes reported in all medical claims to calculate the fraction of each person's diagnoses (i.e., DISEASE_SHARE) that were in each of the following broad disease categories: 1) *Infectious and parasitic diseases* (ICD-9 codes: 001–139); 2) *Neoplasms* (ICD-9 codes: 140–239); 3) *Endocrine, nutritional, metabolic, immunity disorders* (ICD-9 codes: 240–279); 4) *Diseases of the blood and blood-forming organs* (ICD-9 codes: 280–289); 5) *Mental disorders* (ICD-9 codes: 290–319); 6) *Diseases of the nervous system and sense organs* (ICD-9 codes: 320–389); 7) *Diseases of the circulatory system* (ICD-9 codes: 390–459); 8) *Diseases of the respiratory system* (ICD-9 codes: 460–519); 9) *Diseases of the digestive system* (ICD-9 codes: 520–579); 10) *Diseases of the genitourinary system* (ICD-9 codes: 580–629); 11) *Skin and subcutaneous tissue disorders* (ICD-9 codes: 680–709); 12) *Musculoskeletal system and connective tissue disorders* (ICD-9 codes: 710–739); 13) *Congenital anomalies* (ICD-9 codes: 740–759);

14) *Conditions originating in the perinatal period* (ICD-9 codes: 760–779); and 15) *Symptoms, signs, and ill-defined conditions* (ICD-9 codes: 780–799). For example, if all of person *i*'s diagnoses were diabetes (ICD-9: 250), then $DISEASE\_SHARE_{ij} = 1$ if $j = 3$ and $DISEASE\_SHARE_{ij} = 0$ if $j \neq 3$. On the other hand, if this person had three circulatory diagnoses and one digestive diagnosis, then $DISEASE\_SHARE_{ij} = 0.75$ if $j = 7$, $DISEASE\_SHARE_{ij} = 0.25$ if $j = 9$, and $DISEASE\_SHARE_{ij} = 0$ otherwise. Such covariate allowed us to estimate the differences in mortality rates associated with these different diagnosis groups (i.e., allowing relative comparisons across disease categories).

In addition to measuring the shares of diagnoses in each disease category, we generated an index to determine the person's "effective number" of disease categories as follows: $N\_DISEASE\_CATEGORY_i = 1/\Sigma_j\ DISEASE\_SHARE_{ij}^2$

If all of a person's diagnoses fell in one disease category, then $N\_DISEASE_i = 1$. If half of a person's diagnoses fell in one disease category, and half fell in a second category, then $N\_DISEASE_i = 1/(0.5^2 + 0.5^2) = 2$. If 90% of a person's diagnoses fell in one disease category, and 10% fell in a second category, then $N\_DISEASE_i = 1/(0.9^2 + 0.1^2) = 1.22$.

Study Population

To be included in the analysis, patients were required to have continuous health plan coverage, to be ≥65 years old, and to have at least one drug prescription per calendar year. To preserve representativeness throughout the study period, three different birth cohorts, each of the same size, were randomly extracted from the RAMQ database. The first cohort included patients who were 65 years or older as of 1997; the second included patients who met the same criterion as of 1999; and the third group met the age criterion as of 2001. Patients were considered as continuously enrolled if there was no gap in their enrollment exceeding 31 days.

In addition to estimating the model using data on the entire population, we also estimated the model separately for three subpopulations: 1) patients with asthma (ICD-9 code: 493); 2) cancer patients (ICD-9 codes: 140–209); and 3) patients with CVD (ICD-9 codes: 402, 404, 410–414, 425, 428–438, 440, 443–445). We selected these subpopulations in the design phase of our study in light of the recent drug innovation observed for those indications as well as the representativeness of those three diseases in the overall population. To be considered in this analysis, patients were required to have their first diagnosis of the corresponding condition during the first two years of observation.

Statistical Analysis

Estimating the impact of drug vintage on survival. Multivariate analysis was conducted to adjust for potential confounding factors in estimating the impact of drug vintage on patient's survival. The probability of death was analyzed using a time-varying Cox proportional hazards model. In such a model, the hazard of death, or the instantaneous probability that the event will occur, is explicitly parameterized with individual characteristics by using the information included in time-varying covariates. The dependent variable "dead" is an indicator if the person is alive (value 1) or not (value 0) at each specific year of the study. The estimated coefficients are interpreted as the impact on the probability of being dead. A negative coefficient means that an increase in the corresponding variable is associated with longer survival duration or lower probability of being dead. In the case of a dummy variable, the parameter estimate measures the effect on the survival time when the variable goes from zero to one (i.e., changing the status for this variable) controlling for the other covariates of the model. In the case of categorical variables, the parameter estimates are to be interpreted as deviations from the reference category. Finally, in the case of discrete variables, the marginal effect is the impact of a one-unit increase on the hazard of being dead.

Sensitivity Analysis

Sensitivity analyses using alternative regression models were also performed to evaluate the robustness of the study findings. The additional models we estimated included logistic regression modeling the probability of being dead and structural accelerated failure time models using various statistical distributions (e.g., Weibull, Gamma) to assess survival.

Furthermore, we tested the discriminative validity of our model by running an antitest. Specifically, we focused on patients with health conditions for which new medications likely offer quality-of-life benefits, but no survival benefits. A finding that there is no impact of drug vintage on longevity of such patients provides evidence regarding the discriminative validity of our model. We focused on patients with arthritis, mental disorders, and skin problems.

All statistical analyses were performed using SAS release 9.1 or newer (SAS Institute, Inc., Cary, NC).

Results

Study Population Characteristics

The four different patient group dispositions and characteristics are presented in Table 1. The overall population consisted of 102,743 subjects, of which 14,154 (14%) died during the study period. The three other groups of interest were subpopulations having higher percentages of death. Cancer patients had the highest death rate (28%), followed by subjects with CVD (21%).

Mean age of the study population was 68 years, and region and income status disposition were similar over the four groups. The percentage of women differed in the CVD group, which included more men (56%) than the other groups.

The level of health services utilization was highest in the cancer group. The entire study population had an average of 14 outpatient consultations per year, 9 (64%) of which were with a specialist. The entire population had 47 prescriptions per year on average, which was smaller than the average in each of the three specific disease groups. The patients suffered from 2.4 different "effective" disease categories, on average, as previously defined. The disease breakdown showed that infectious and parasitic diseases and circulatory system problems were the primary illness categories.

Drug Vintage Statistics

Table 2a,b shows the most prescribed ingredients during the study period. In Table 2a, the 10 most prescribed ingredients are presented for each of the distinct drug vintage categories. The 2000 to 2006 category was combined with the 1990 to 1999 group for the multivariate analysis as their shorter observable period (2000–2006) resulted in a limited use of these drugs (i.e., <3% of total dispensing; see Table 1).

It is worth noting that the ingredients presented in Table 2a are also reported in the IMS Health Canada "Top 200 drugs dispensed in Canada" publications from 2000 to 2006 [17]. Every year, IMS Health Canada publishes a list of the most utilized drugs in Canada and approximately 70% of the ingre-

Table 1 Study population characteristics

	Overall population	Asthma	Cancer	CVD
Study population disposition				
Number of subjects	102,743	6,912	12,341	29,394
Observation period (year), mean (SD)	8.6 (2.2)	8.6 (2.3)	7.5 (3.0)	8.3 (2.5)
Mortality rate, n (%)	14,154 (14)	1,220 (18)	3,479 (28)	6,043 (21)
Cohort				
1997, n (%)	36,269 (35)	2,503 (36)	4,759 (39)	11,238 (38)
1999, n (%)	33,784 (33)	2,315 (33)	3,879 (31)	9,660 (33)
2001, n (%)	32,690 (32)	2,094 (30)	3,703 (30)	8,496 (29)
Demographics				
Age, mean (SD)	68 (1.7)	68 (1.7)	68 (1.8)	68 (1.7)
Female, n (%)	60,742 (59)	4,410 (64)	6,381 (52)	13,164 (44)
Region, n (%)				
Montreal	24,791 (24)	1,883 (27)	3,138 (25)	7,089 (24)
Quebec	9,260 (9)	562 (8)	1,073 (9)	2,717 (9)
Mauricie	7,633 (7)	332 (5)	811 (7)	2,085 (7)
Monteregie	15,509 (15)	1,133 (16)	1,975 (16)	4,482 (15)
Other	40,493 (39)	2,647 (38)	4,672 (38)	11,352 (38)
Government GIS status, n (%)				
Full GIS	3,265 (3)	208 (3)	385 (3)	785 (3)
Partial GIS	42,865 (42)	2,297 (33)	4,493 (36)	9,792 (33)
Without GIS	56,600 (55)	4,407 (64)	7,460 (60)	18,815 (64)
Yearly medical and drug utilization, mean (SD)				
Inpatient hospitalization admission*	0.3 (0.6)	0.6 (1.1)	0.7 (1.4)	0.6 (1.1)
Inpatient length of stay, days	2.7 (6.71)	4.5 (9.4)	5.1 (10.8)	4.5 (8.9)
Outpatient consultation*	14 (10.39)	20 (12.4)	21 (14.3)	18 (13.7)
Specialist consultation	9 (8.90)	12 (10.6)	15 (13.2)	12 (12.6)
Drug utilization, prescription†	47 (29.16)	61 (37.4)	50 (31.8)	65 (34.7)
Drug vintage, % of medication use				
Pre-1970	30	32	33	34
1970–1979	14	16	15	13
1980–1989	19	16	20	19
1990–1999	34	35	31	33
2000–2006	2	2	1	2
Comorbidities				
Number of disease, mean (SD)	2.4 (0.9)	2.8 (0.9)	2.7 (0.9)	2.6 (0.9)
Number of disease category, %				
0	5	2	2	2
1	22	14	16	19
2	31	28	30	31
3	23	27	25	25
4	13	18	16	14
≥5	7	12	10	9
Disease category‡, %				
Infectious and parasitic diseases	66	78	74	71
Neoplasms	18	21	66	20
Endocrine, nutritional, metabolic, immunity	29	28	29	33
Mental disorders	15	19	17	15
Nervous system and sense organs	31	35	33	33
Circulatory system	51	55	53	79
Respiratory system	28	67	32	33
Digestive system	17	23	22	20
Genitourinary system	23	26	27	23
Skin and subcutaneous tissue	15	18	19	16
Musculoskeletal system and connective tissue	32	40	34	33
Symptoms, signs, and ill-defined conditions, %	35	52	44	44

*Inpatient hospitalizations refer to any hospitalizations and emergency-room visits lasting more than 1 day. Outpatient consultations refer to any hospitalizations and emergency-room visits lasting no more than 1 day, plus physician outpatient visits.
†Prescriptions were normalized to 28 days of therapy.
‡Reported as annual rates.
CVD, cardiovascular disease; GIS, guaranteed income supplement.

dients listed in our Table 2a appear in the IMS Health Canada publications under a generic or brand drug name. This suggests that the patient profile of users in this study is somewhat comparable to the Canadian population.

The top 20 prescribed ingredients are also presented for each subpopulation of interest in Table 2b. The ingredients for asthma and CVD reported in Table 2b are representative of the treatments available on the market. Ingredients for the cancer population are treatments used before and after a cancer for prevention or to recover from side effects linked to chemotherapy. Unfortunately, chemotherapy agents administered in the inpatient/hospital setting are not available from the RAMQ database, which explains why commonly used regimens are not reported in Table 2b for this subpopulation.

Survival Analysis

The Cox regression coefficients and hazard ratios (HR) (i.e., hazard of dying) are presented in Table 3a. The results indicated that women have longer survival duration, with an HR of 0.598 of dying compared with men. Patients with full to partial GIS have a higher risk of dying than patients without GIS, suggesting that patients with a higher income have a higher life expectancy.

Table 2 (a) Most prescribed active ingredients, stratified by drug vintage category. (b) Most prescribed active ingredients, stratified by disease group

(a)

Active ingredient	Drug vintage	% of prescriptions for the category
Drug vintage: Pre-1970		
Acetylsalicylic acid	Dec-10	17
Hydrochlorothiazide	Dec-59	13
Levothyroxine sodium	Dec-51	12
Conjugated estrogens	Dec-51	8
Calcium	Dec-51	5
Vitamin D3	Dec-51	4
Furosemide	Dec-66	3
Medroxyprogesterone acetate	Dec-60	3
Warfarin sodium	Dec-57	3
Acetaminophen	Dec-49	3
Drug vintage: 1970–1979		
Lorazepam	Dec-77	18
Metoprolol tartrate	Dec-77	15
Glyburide	Dec-71	14
Oxazepam	Dec-72	8
Clonazepam	Dec-77	6
Salbutamol	Dec-72	6
Flurazepam hydrochloride	Dec-71	4
Estradiol	Dec-76	3
Timolol	Dec-79	3
Propranolol hydrochloride	Dec-74	2
Drug vintage: 1980–1989		
Atenolol	Dec-88	11
Diltiazem hydrochloride	Dec-88	9
Nifedipine	Dec-82	9
Omeprazole	Dec-89	8
Enalapril maleate	Dec-87	6
Indapamide	Dec-82	6
Triamterene	Dec-81	5
Acebutolol hydrochloride	Dec-86	4
Ipratropium bromide	Dec-83	4
Alprazolam	Dec-81	3
Drug vintage: 1990–1999		
Atorvastatin	Mar-97	11
Metformin hydrochloride	Dec-93	7
Amlodipine	Dec-92	6
Simvastatin	Dec-90	5
Ramipril	Dec-93	4
Pravastatin sodium	Dec-90	4
Alendronic acid	Dec-96	3
Pantoprazole	Mar-97	3
Irbesartan	Jun-98	3
Lisinopril	Dec-90	3
Drug vintage: 2000–2006		
Esomeprazole	Aug-01	21
Rosuvastatin	Feb-03	19
Bisoprolol fumarate	Jun-00	15
Rosiglitazone	Mar-00	8
Tiotropium	Nov-02	5
Alfuzosin hydrochloride	Feb-02	4
Rabeprazole sodium	Apr-02	4
Ezetimibe	Jun-03	4
Pioglitazone	Aug-00	3
Mirtazapine	May-01	2

Table 2 Continued

(b)

Active ingredient	Drug vintage	% of prescriptions for the population
Asthma subpopulation		
Fluticasone propionate	Mar-93	4.1
Acetylsalicylic acid	Dec-10	4.0
Levothyroxine sodium	Dec-51	4.0
Hydrochlorothiazide	Dec-59	3.4
Salbutamol	Dec-72	3.2
Conjugated estrogens	Dec-51	2.8
Atorvastatin	Mar-97	2.8
Lorazepam	Dec-77	2.2
Diltiazem hydrochloride	Dec-88	2.0
Ipratropium bromide	Dec-83	1.9
Salmeterol	Dec-94	1.9
Omeprazole	Dec-89	1.7
Amlodipine	Dec-92	1.6
Metformin hydrochloride	Dec-93	1.6
Calcium	Dec-51	1.6
Furosemide	Dec-66	1.4
Vitamin D3	Dec-51	1.4
Budesonide	Dec-90	1.3
Pantoprazole	Mar-97	1.2
Alendronic acid	Dec-96	1.2
Cancer subpopulation		
Levothyroxine sodium	Dec-51	5.5
Acetylsalicylic acid	Dec-10	4.8
Atorvastatin	Mar-97	4.2
Hydrochlorothiazide	Dec-59	3.7
Lorazepam	Dec-77	2.4
Conjugated estrogens	Dec-51	2.1
Metformin hydrochloride	Dec-93	2.0
Amlodipine	Dec-92	1.7
Omeprazole	Dec-89	1.7
Pravastatin sodium	Dec-90	1.7
Simvastatin	Dec-90	1.6
Atenolol	Dec-88	1.6
Alendronic acid	Dec-96	1.6
Metoprolol tartrate	Dec-77	1.6
Calcium	Dec-51	1.6
Vitamin D3	Dec-51	1.5%
Diltiazem hydrochloride	Dec-88	1.5
Nifedipine	Dec-82	1.4
Glyburide	Dec-71	1.3
Tamoxifen	Dec-86	1.2
Cardiovascular disease subpopulation		
Acetylsalicylic acid	Dec-10	8
Atorvastatin	Mar-97	6
Levothyroxine sodium	Dec-51	3
Hydrochlorothiazide	Dec-59	3
Diltiazem hydrochloride	Dec-88	3
Metoprolol tartrate	Dec-77	3
Simvastatin	Dec-90	2
Atenolol	Dec-88	2
Amlodipine	Dec-92	2
Metformin hydrochloride	Dec-93	2
Pravastatin sodium	Dec-90	2
Lorazepam	Dec-77	2
Furosemide	Dec-66	2
Nitroglycerin	Dec-64	2
Conjugated estrogens	Dec-51	2
Warfarin sodium	Dec-57	2
Ramipril	Dec-93	2
Nifedipine	Dec-82	2
Glyburide	Dec-71	1
Omeprazole	Dec-89	1

Patients who have been hospitalized are more likely to die. Each additional hospital admission per year is associated with a 16.4% increase in the risk of dying. Furthermore, patients with 1 to 5 "effective" diseases are 1.5 to 4.6 times more likely to die compared with those in good health (i.e., no "effective" disease). Similarly, patients requiring specialist consultation face an 18% increase in the risk of dying relative to those patients without specialist consultation during the year. As might be expected with an elderly population, a diagnosis of cancer (neoplasm) significantly increased the risk of mortality. Interestingly, after controlling for the occurrence of specialist consultation, the number of outpatient visits to any physician has an opposite impact on hazard risk. Every consultation is associated with a 1% reduction in the risk of dying, suggesting that a sustained follow-up by a physician is beneficial for elderly people to control and recover their health. Such follow-up might also allow patients to have access to appropriate medication and significantly increases survival time.

Table 3 (a) Multivariate Cox regression model using time-varying covariates. (b) Multivariate Cox regression model using time-varying covariates—adjusted impact of drug vintage on survival, stratified by disease group*

(a)

Variable	Parameter estimate	Hazard ratio (HR)	95% HR confidence limit	*P*-value
Drug vintage				
Pre-1970 (reference)	—	—	—	—
Post-1970	0.283	1.328	[1.213; 1.453]	<0.0001
Post-1980	−0.349	0.706	[0.639; 0.779]	<0.0001
Post-1990	−0.651	0.522	[0.476; 0.572]	<0.0001
Demographics				
Age	0.178	1.195	[1.182; 1.209]	<0.0001
Female	−0.514	0.598	[0.576; 0.620]	<0.0001
Year dummies				
1997 (reference)	—	—	—	—
1998	−0.168	0.846	[0.704; 1.015]	0.0725
1999	0.364	1.439	[1.219; 1.699]	<0.0001
2000	0.019	1.019	[0.858; 1.210]	0.8275
2001	0.377	1.458	[1.234; 1.722]	<0.0001
2002	0.337	1.400	[1.180; 1.662]	0.0001
2003	0.187	1.205	[1.008; 1.441]	0.0401
2004	0.101	1.106	[0.921; 1.328]	0.2816
2005	−0.054	0.947	[0.784; 1.145]	0.5741
2006	−0.318	0.728	[0.597; 0.888]	0.0017
Government GIS status				
Full GIS	0.216	1.241	[1.129; 1.364]	<0.0001
Partial GIS	0.012	1.012	[0.974; 1.051]	0.5371
Without GIS (reference)	—	—	—	—
Region				
Montreal	−0.038	0.963	[0.921; 1.005]	0.0860
Quebec	0.028	1.029	[0.965; 1.096]	0.3872
Mauricie	−0.355	0.701	[0.649; 0.757]	<0.0001
Monteregie	0.021	1.021	[0.971; 1.074]	0.4122
Other (reference)	—	—	—	—
Yearly medical resources utilization				
Inpatient hospitalization frequency	0.151	1.164	[1.156; 1.171]	<0.0001
Inpatient length of stay	0.017	1.017	[1.017; 1.018]	<0.0001
Outpatient consultation frequency	−0.008	0.992	[0.990; 0.993]	<0.0001
Specialist consultation (yes/no)	0.168	1.183	[1.104; 1.267]	<0.0001
Number of prescription	−0.016	0.984	[0.983; 0.985]	<0.0001
Comorbidities				
Number of disease category				
No disease (reference)	—	—	—	—
1 disease	0.406	1.501	[1.137; 1.981]	0.0041
2 diseases	0.797	2.218	[1.683; 2.923]	<0.0001
3 diseases	1.106	3.021	[2.291; 3.983]	<0.0001
4 diseases	1.400	4.056	[3.072; 5.354]	<0.0001
≥5 diseases	1.537	4.653	[3.518; 6.154]	<0.0001
Disease category				
Infectious and parasitic diseases	−3.011	0.049	[0.035; 0.069]	<0.0001
Neoplasms	2.210	9.113	[7.035; 11.806]	<0.0001
Endocrine, nutritional, metabolic, immunity	−1.573	0.207	[0.156; 0.276]	<0.0001
Mental disorders	−1.005	0.366	[0.273; 0.490]	<0.0001
Nervous system and sense organs	−2.816	0.060	[0.044; 0.081]	<0.0001
Circulatory system	−0.419	0.658	[0.506; 0.854]	0.0017
Respiratory system	0.177	1.194	[0.912; 1.563]	0.1974
Digestive system	−1.089	0.337	[0.248; 0.457]	<0.0001
Genitourinary system	1.546	4.694	[3.526; 6.250]	<0.0001
Musculoskeletal system and connective tissue	−0.242	0.785	[0.583; 1.057]	0.1110
Symptoms, signs, and ill-defined conditions	3.677	39.528	[30.735; 50.837]	<0.0001
Regression information				
Likelihood ratio: <0.0001				
Number of patient-year observations: 859,858				
Total number of events: 13,084				

(b)

Overall population (N = 102,743)				
Pre-1970 (reference)	—	—	—	—
Post-1970	0.283	1.328	[1.213; 1.453]	<0.0001
Post-1980	−0.349	0.706	[0.639; 0.779]	<0.0001
Post-1990	−0.651	0.522	[0.476; 0.572]	<0.0001
Post-1970 vs. pre-1970	−0.717	0.488		

Table 3 Continued

Asthma subpopulation (n = 6,912)				
Pre-1970 (reference)	—	—	—	—
Post-1970	−0.395	0.674	[0.470; 0.966]	0.0318
Post-1980	0.225	1.252	[0.837; 1.873]	0.2735
Post-1990	−1.082	0.339	[0.236; 0.486]	<0.0001
Post-1970 vs. Pre-1970	−1.252	0.286		
Cancer subpopulation (n = 12,341)				
Pre-1970 (reference)	—	—	—	—
Post-1970	0.246	1.279	[1.080; 1.515]	0.0044
Post-1980	−0.359	0.699	[0.584; 0.836]	<0.0001
Post-1990	−0.754	0.471	[0.393; 0.564]	<0.0001
Post-1970 vs. Pre-1970	−0.867	0.420		
CVD subpopulation (n = 29,394)				
Pre-1970 (reference)	—	—	—	—
Post-1970	−0.021	0.979	[0.833; 1.151]	0.8010
Post-1980	−0.488	0.614	[0.514; 0.733]	<0.0001
Post-1990	−0.610	0.543	[0.462; 0.638]	<0.0001
Post-1970 vs. Pre-1970	−1.119	0.327		

*The drug vintage coefficient estimates presented in this table were generated from the same regression model as reported in Table 3a, controlling for year indicator variables and patient-specific age, sex, region of residence, low income status, medical services use, concomitant drug use, and comorbidities.
CVD, cardiovascular disease; GIS, guaranteed income supplement

Demographic characteristics, GIS status, region, medical and drug resources utilization, and comorbidity results from asthma, cancer, and CVD sub-analyses had similar impacts on survival time (results not shown here; available upon request).

Impact of Drug Vintage on Survival

The results of the impact of drug vintage on patients' probability of survival are reported in Table 3b. For each population, the Pre-1970 period was the reference category in the regression model. The results of this analysis consistently indicated that the use of Post-1990 ingredients significantly reduced the risk of mortality. These findings suggest that recent drug innovation, in particular Post-1990 medications, had a significant beneficial impact on the survival of patients.

When the cumulative impact of newer drugs on the hazard of dying (i.e., $\beta_{\text{Post-1970}} + \beta_{\text{Post-1980}} + \beta_{\text{Post-1990}}$: Post-1970 vs. Pre-1970 medications) was calculated, the results indicated that the introduction of the new treatments in the last three decades reduced the risk of mortality by 51% for the overall population (HR: 0.488 for Post-1970 medication relative to Pre-1970). This finding was even stronger for the subpopulation analyses (asthma: HR = 0.286; cancer: HR = 0.420; CVD: HR = 0.327).

To illustrate the impact of drug vintage on mortality, we plotted the survival curves based on the estimated drug vintage regression coefficients (evaluated at the sample means for the other covariates), assuming that a patient would consume only 1) Post-1990; 2) 1980 to 1989; 3) 1970 to 1979; and 4) Pre-1970 medications. Figure 1 clearly demonstrates that recent drugs (i.e., marketed after 1990) had a substantial contribution to improving patients' survival. The results for the CVD subpopulation (Fig. 1d) highlight how drug innovation has constantly and markedly reduced mortality in this specific disease group population. The estimated 10-year mortality rate according to vintage category steadily declined between the Pre-1970 and the Post-1990 categories, dropping from 16.8% to 5.8%, respectively.

Sensitivity Analysis

The results of the sensitivity analyses using alternative regression models corroborated the study conclusion (results not shown here; available upon request). The logistic model for the overall population indicated that the utilization of Post-1990 ingredients was associated with a 49% (95% confidence interval: 43–54%) reduction in the risk of mortality, as compared with older ingredients. Based on the structural accelerated failure time models, the results revealed that the use of recent drugs was consistently associated with a statistically significant increase in longevity using various statistical distributions (Weibull, Gamma, and log-logistic).

Finally, the anti-test results provided further evidence of the discriminative validity of our model (Fig. 2). As expected, the findings from the model based on patients with arthritis, mental disorder, or skin problems indicated no appreciable survival benefit for recent medications (i.e., no drug vintage impact), as compared with the overall population and the subpopulations (Fig. 1). These results suggest that our model accurately predicts the survival impact of drug vintage, as demonstrated by these conditions where medications may be intended to improve patients' quality of life and are not expected to yield longevity gains.

Discussion

In his article on the effect of drug vintage on survival, Lichtenberg reported that the Puerto Rico Health Insurance Administration (ASES) beneficiaries using new ingredients were less likely to die [16]. The estimated mortality rates from Pre-1970 to Post-1990 decreased from 4.4% to 2.5%, respectively.

The present study investigated drug vintage impact on the survival time of elderly RAMQ beneficiaries. In contrast to Lichtenberg's methodology, a Cox regression model using time-varying covariates was used for the analysis. Using medical and pharmacy claims from the RAMQ database, drug vintage, which was measured using the Health Canada database, showed a positive and significant impact on survival time, with only one exception, the Post-1970 vintage category (i.e., drugs introduced between 1970 and 1979). Mortality rates (similar to ASES beneficiaries) found for Pre-1970, 1970 to 1980, 1980 to 1989, and Post-1990 drug vintage categories were 7.6%, 9.9%, 7.1%, and 3.8%, respectively.

In addition to estimating the model using data on the entire population, we also examined three specific disease groups (asthma, cancer, and CVD). Models estimated using data on asthmatics showed important survival benefits for 1970 to 1979

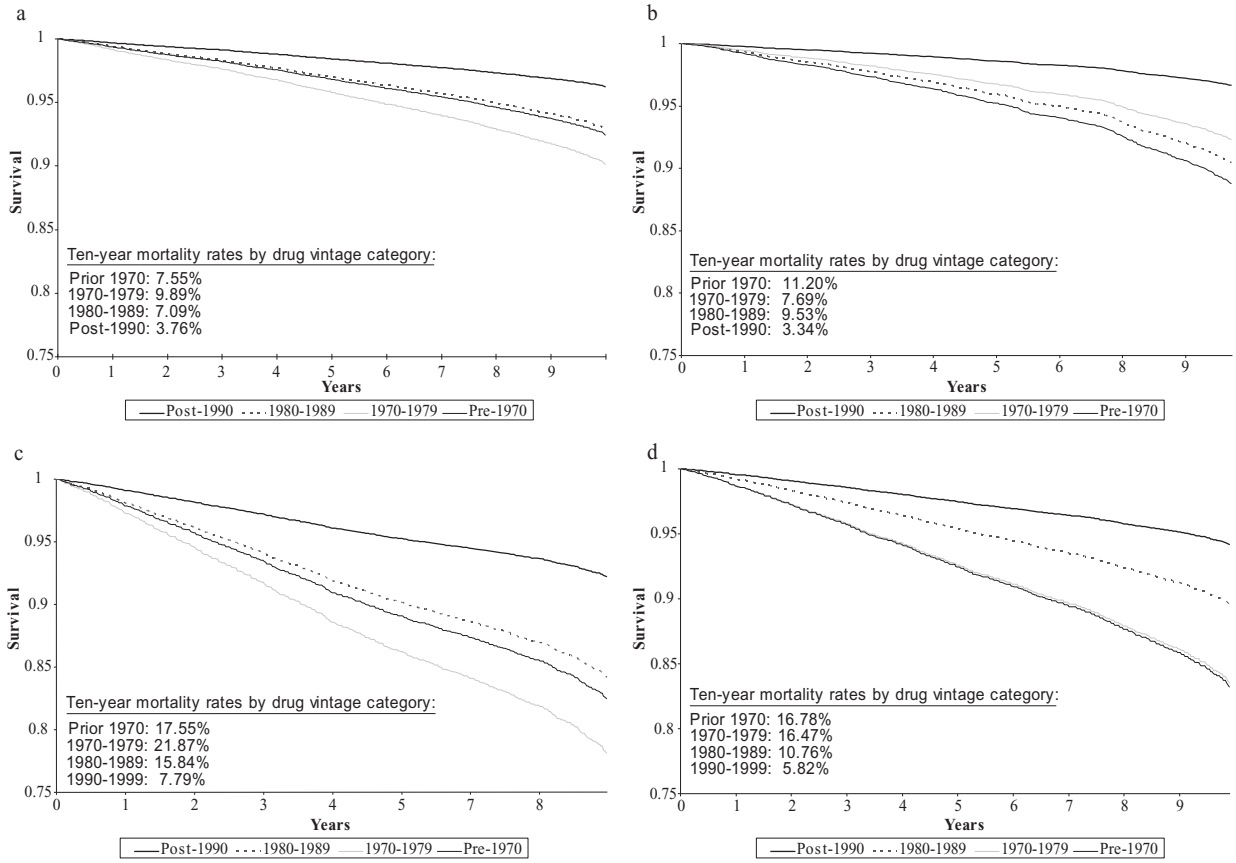

Figure 1 (a) Estimated survival curves by drug vintage use: overall population. (b) Estimated survival curves by drug vintage use: asthma subpopulation. (c) Estimated survival curves by drug vintage use: cancer subpopulation. (d) Estimated survival curves by drug vintage use: cardiovascular disease subpopulation.

and Post-1990 ingredients. Interestingly, these two periods coincide with periods of major innovations in asthma treatment [18,19]. During the 1970s, short-acting β_2-adrenergic receptor agonists used for the relief of bronchospasm were improved. For instance, salbutamol (Ventolin, GlaxoSmithKline, London, UK) was introduced in 1972. This drug is similar to epinephrine (adrenaline), but without all its side effects [20]. During the following two decades, research focused essentially on prevention instead of control or symptom reduction. There was no significant innovation in the 1980s, with the sole exception of

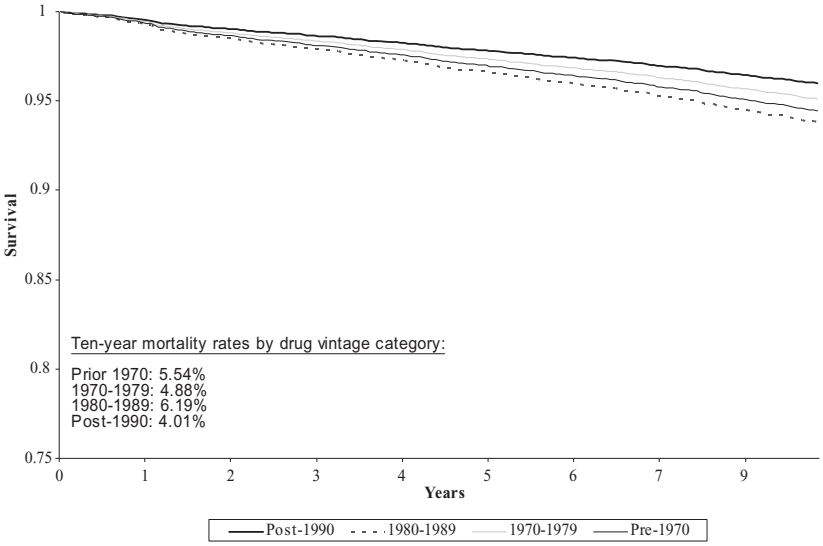

Figure 2 Anti-test: estimated survival curves by drug vintage use for patients with arthritis, mental disorder, or skin problems.

ipratropium bromide (Atrovent, Boehringer Ingelheim, Ingelheim, Germany). The second major innovation in this therapeutic area happened in the 1990s [20], when inhaled corticosteroids and corticosteroid pills were launched.

The cancer subpopulation rendered similar results as the overall population model. One important reason that could explain the mitigated results for the drugs marketed between 1970 and 1990 is the fact that many effective chemotherapy treatments administered to cancer patients are given in the inpatient/hospital setting. Such information regarding treatments administered to patients at the hospital is not available in the RAMQ database. Our data cover primarily preventive and recovery drugs, which are prescribed in an outpatient setting. To illustrate this issue, only one chemotherapy treatment was reported among the top ingredients prescribed to cancer patients in our sample (tamoxifen for breast cancer treatment). Consequently, our model was unable to precisely measure the benefits of recent chemotherapy agents in this population, which most likely resulted in conservative estimates of the impact of drug vintage on survival. Nevertheless, some specific ingredients can be administered for prevention or health stabilization after chemotherapy treatments, but that may not be the primary reason for their dispensing. For example, metformin hydrochloride is one of the primary recent (Post-1990) antidiabetic drugs used in the treatment of diabetes mellitus type 2 that has been shown to prevent colon or breast cancer in patients with diabetes [21,22].

With respect to CVD, the understanding of heart disease and associated cardiac outcomes has evolved over the last century. A better understanding of CVD problems has allowed researchers to focus on prevention to stabilize cardiac outcomes [23]. In the early 1970s, studies showed for the first time a link between hypertension and heart problems. Even though scientists were aware of this association, it took time for traditional treatments to be modified. Furthermore, it was only as recently as the early 1990s that new research on treating elderly patients for blood pressure showed that prevention for CVD complications is even more effective for elderly patients than for younger ones [24]. In addition, a number of clinical trials have highlighted a positive correlation between cholesterol reduction and a reduction in coronary heart disease risk; cholesterol-lowering drugs (statins) were introduced during the 1990s [25]. Our model reflects the reduction of mortality rate attributable to these drug innovations.

Although claims data are a rich source of information on health care and drug utilization, there are some inherent limitations. Pharmacy-claims data do not provide any information on patients' compliance. Also, claims data are subject to coding errors making it difficult to identify underlying health problems and disease severity. In estimating our model, however, we attempted to control for patients' illnesses by including many covariates that are correlated with the disease severity. Despite our attempt to control for all confounding factors, it is possible that other important determinants such as the "quality of prescriber" and the level of education also influenced the relationship between drug innovation and survival. For example, it could be argued that more skilled physicians prescribe newer drugs and patients treated by such skilled physicians live longer. Even though we tried to eliminate this potential bias by controlling for the occurrence of specialist consultation or not, there might be residual effects that the model is not capturing. Unfortunately, education, type of work, environmental, and lifestyle (drinker, smoker status, etc.) variables that are also important determinants of health status were not available in the database. It is also possible that patients taking newer medications are likely to be more health conscious, thus living longer than those taking older medications (creating endogeniety bias). Nevertheless, it is important that, if this were true (i.e., healthier patients using newer drugs or better physicians prescribing newer drugs), we would find that newer medications are always better; however, we found that the survival benefits varied with the period of introduction for the asthma subpopulation, suggesting that endogeniety bias might be negligible. Furthermore, the substantial innovations made in surgery over the past three decades that have greatly contributed to patients' health status, thus life expectancy, might be positively correlated with drug vintage. It is unclear whether this is indeed the case; however, if patients taking newer medications are more likely to have surgery, the impact of drug innovation may be overestimated. Nevertheless, it should be noted that these limitations are present in any study conducted with claims data and are not specific to the present study. Lastly, it is important to mention that the current study did not address the policy implication, that is, by assessing the value received for the money spent on newer prescription drugs. We intend to address this question in future research.

Despite these limitations, our study had the advantage of relying on patient-level information in estimating the impact of drug vintage on patients' survival. The complete claims history allowed for adjustment of important confounding factors that may otherwise bias the estimated impact of drug innovation. Our study population was based on relatively healthy seniors from Quebec, rendering a high generalizability of the study results.

Conclusion

The results of this analysis provide strong support for the hypothesis that recent drug innovation, in particular medications launched after 1990, had a significant beneficial impact on the survival of elderly Canadians. Our model also accurately predicted the reduction of the mortality rate attributable to newer agents used in the treatment of asthma and CVD.

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Supporting information for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

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